July 11, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 97N-0497 Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products; Request for Comments

Dear Sir or Madam:

We are responding to docket 97N-0497 specifically in the area of unrelated donor cord blood banking. The St. Louis Cord Blood Bank has been active in cord blood banking since 1996 and has been working under FDA IND 7183 since 12/97. Additionally, our companion stem cell transplant program at Cardinal Glennon Children's Hospital has performed about 40 unrelated donor cord blood transplants during that time period.

We give the FDA permission to use all information provided under the IND process, with the exception of the clinical transplant protocol (which is a collaborative effort with other transplant teams), for use in the development of product standards. Additionally, should it be helpful to the FDA, we are willing to share data files on banked cords and transplant outcomes.

In response to the docket, we would like to address several areas that we feel are important in cord blood banking, and pertain to this product standards process.

We fully support the accreditation efforts that have been developed by the Foundation for the Accreditation of Hematopoietic and Cellular Therapies (FAHCT). Members of our team have been active in the process of standard development and will participate actively in the site visit process. These standards cover all aspects of the cord blood procedure, from collection, through processing and banking, and finally release for infusion. They complement established accreditation procedures for stem cell laboratories and clinical transplant programs. In a field as dynamic as that of stem cell transplantation, those active in the field are the best able to both develop standards and ensure their enforcement.

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Over the past nearly 5 years of our program, we have seen many changes and improvements in both our product process and clinical transplantation. There several areas that we would like to comment on which pertain to the development of regulations for cord blood banking.

Community-based cord blood collections:
From the inception of our program, we have worked with community obstetricians and delivery units for the collection and initial labeling of the cord blood units. We have developed a comprehensive program of education, process control and quality control for collection by obstetricians. Our approach fundamentally means that the first steps of production are not performed by employees of the bank. However, we believe that our careful education and quality control process, combined with the utilization of medical professionals trained in similar tasks (delivery of infants, proper transfusion labeling, cannulization of the umbilical vein) results in the collection of a reliable product. In addition, this approach allows us to reach smaller communities that would otherwise not be able to contribute to the cord blood pool. Our standard operating procedures, part of the IND application, detail our methodology.

Bacterial contamination of cord blood:
The nature of cord blood collection is such that contamination of the product from organisms that colonize maternal skin and vagina is an inherent risk. Thus bacterial culturing in important. We have worked on optimal culturing approaches which address the limited volume of cord blood and the need to perform end processing cultures. From 1/00 to 7/00 we have been performing optimal culture volume aerobic and anaerobic cultures with processing discard and final product aerobic cultures prospectively. Only 3/300 products were consistently culture positive in all 3 cultures – supporting contamination of the initial product.

The greater question is what to do with the information. By the time the culture results are obtained the cord blood unit has been processed and frozen. In bone marrow transplantation it is not uncommon that bone marrow collections are found to be bacterial culture positive (usually coagulase negative staphylococcus) and infectious complications from infusing the product are rare. We have taken the approach of discarding products that are contaminated with fungus or organisms that are associated with serious bacterial infections (contaminant being gram negative organism). The rest of the units are saved, as is a sample of the bacterial isolate (for performing antibiotic sensitivities if needed). The culture result is reported to potential transplant centers as part of the comprehensive report that is released to the transplant center prior to confirmatory testing. We have looked retrospectively at the outcome of 2/120 transplants performed with units released from our bank that were culture positive at the end of processing.

ID	CBU bacterial culture (post-processing)	CBU bacterial culture (post-thaw)	Outcome Recipient post-transplant infection (first 3 months post transplant)
60	Diptheroids	negative	negative
67	Coagulase neg staphylococcus	negative	negative (verbal report)

Minimum volume/nucleated cell count for banking:
While in general the larger cord blood units contain more cells and result in a product more useful to a larger percentage of the population, small cord blood units may have adequate cell doses for infants. Thus we would not regulate cord blood processing based on a minimum volume. Since 1998 it has been our practice to bank only cords above 50 ml and containing 800 x 10^6 cells. This practice evolved because of limited financial resources on our part and not from regulatory conscience. We have noted that with increasing minimal cell volume and cell number criteria over the years we are banking a lower percentage of cord blood units collected.

Table 1. Impact of raising minimum cord blood banking criteria on the percentage of collected cord blood units that are banked

Time period	Minimum banking criteria	% of collected cords banked
01/96-07/96	Volume 40 ml TNC 600 x 10^6	48% 200/389 collected
08/96-10/97	Volume 40 ml TNC 700 x 10^6	39% 1857/5030 collected
11/97-06/99	Volume 50 ml TNC 800 x 10^6	24% 2164/9049 collected

Our opinion is that the minimum collected volume or cell count criteria for banking is more a financial decision than a product safety decision. There may be instances where smaller cords are banked in attempt to gain greater immunologic heterogeneity of products.

However it is important that, as part of product processing monitoring, excessive cell loss during processing, especially if associated with decreased cell viability, be evaluated. If a large number of cord blood cells are lost during processing, then the possibility of losing hematopoietic progenitors unequally is present. In review of over 4,000 cord blood units processed, our average yield of cells post processing is 90% of the initial cells collected. In an analysis of 30 cord blood units prospectively, over 95% of CD34+ cells are retained within the banked product. Some of the cell loss is nucleated red blood cells that do not contribute to engraftment.

Table 2: Yields pre- and post-processing for Total Nucleated Cell Count (TNC), CD34, and NRBC*:

	TNC (x10^6 cells)		CD34 (x 10^6 CD34$^+$ cells)		NRBC (x10^6 cells)	
	pre	post	pre	post	pre	post
Median	1116	946	4.4	4.4	121	67
Min.	684	660	1.0	1.0	21	17
Max.	2400	2278	19.3	15.8	362	217
Recovery (%)		87		97		69

* *There were 30 paired samples.*

Table 2. Yield of Total Nucleated cells with processing (n=4055)

	TNC (x10^6 cells)		TNC	Volume (ml)		
	Pre-	Post-	(% recovery)	Pre-	Post-	% reduction
Mean	1276	1141	90	109	28	74
Median	1155	1044	90	105	27	74
SD	479	399	5.6	23	5	4
Min.	403	295	55	56	16	43
Max.	5960	4700	100	246	62	85

* Yields obtained on routine cord blood units consecutively processed from 5/96 thru 3/2000.

Storage temperature:

Given that cord blood is going to be stored for many years, we have elected to store in liquid nitrogen to minimize temperature exposure in ranges that could result in cell damage. We have been tracking the impact of length of storage on the ability of the cord blood unit to engraft and on transplant survival. Shown below are neutrophil and platelet engraftment for cord blood units that have been stored >2 years, 1-2 years and less than 1 year. At this time there is no difference in engraftment or survival. Clearly this is not the length of storage that is of interest, but we are not seeing a trend in engraftment time, which we believe would be the most sensitive indicator of loss of product viability.

Figure 1: Impact of length of storage of cord blood unit on neutrophil recovery

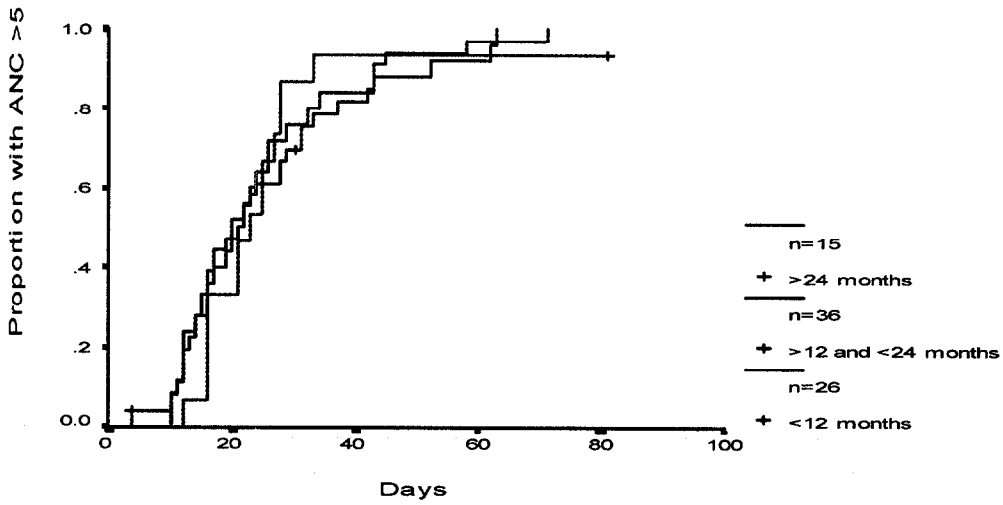


Figure 2: Impact of length of cord blood unit storage on platelet recovery post transplant

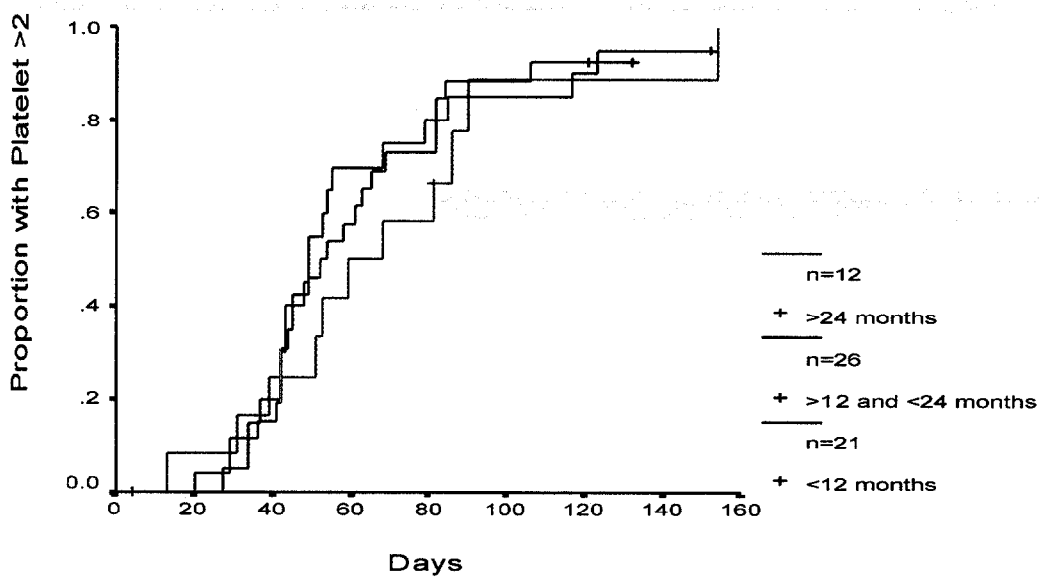
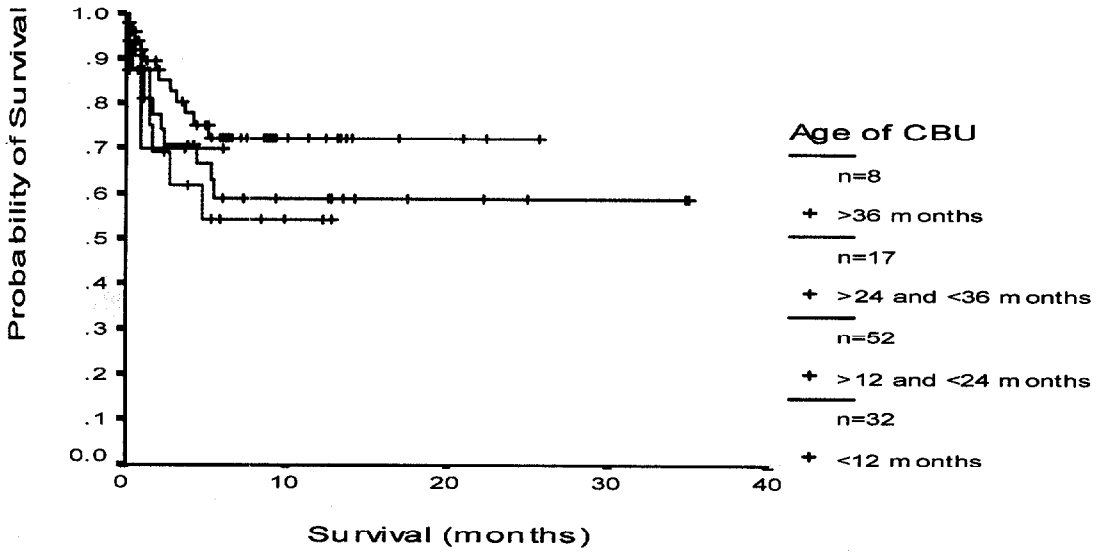


Figure 3: Impact of length of cord blood unit storage on survival post transplant



Correlation between nucleated cell count, CD34+ enumeration, and CFU analysis:

Central to our evaluation of cord blood as an alternative stem cell source is the assessment of hematopoietic potential. We routinely perform total nucleated cell count, $CD34^+$ enumeration, total CFU, and more recently quantitation of nucleated red blood cells (NRBC). We, as others, have noted a linear correlation between all 3 measures of hematopoiesis. However this correlation breaks down at lower CD34 and CFU quantitation. This lack of linearity at the lower cell counts may be due to inaccuracy of the CD34 analysis in the lower range, possibly CD34 negative hematopoietic precursors. The purpose of the analysis is to identify products with a lower hematopoietic potential that would be expected for a given cell count. In appendix 3 we present a draft of a manuscript that we are writing which addresses this issue.

Minimum nucleated cell count for transplantation:

There is a growing appreciation that cell dose is very important and correlates directly with time to engraftment and survival. In the attached appendices we present our experience with the cord blood units used in transplantation from the St. Louis Cord Blood Bank (appendix 1) and the experience of the Stem Cell Transplant Program at Cardinal Glennon Children's Hospital (appendix 2). The cord blood transplants performed at Cardinal Glennon have utilized cord blood units from the St. Louis Cord Blood Bank (n=25), New York Placental Blood

Program (n=14), and the Milan Cord Blood Bank (n=2). Our engraftment and survival evaluation is hampered by few transplants being performed for cell dose less than 2 x10^7/kg – clearly a transplant program practice at present. Based on our analysis we have better outcomes for transplants performed with cell doses greater than 3 x 10^7/kg, but have too few transplants below that threshold to be firm about a lower limit. Ongoing analysis of CD34+ cells/kg will be forwarded to the FDA under separate cover.

Impact of HLA typing

For information we also include our analysis of the impact of HLA matching on survival for both cohorts (appendix 1 and 2). We are not able to detect a statistically significant difference between HLA 6/6, 5/5, or 4/6 transplants at this point. Our sample size is insufficient to answer this crudely. This issue is further complicated by the heterogeneity of differences in the HLA matching and the limited knowledge of the clinical significance of specific mismatches. At our program we are comfortable offering 4/6, and in selected instances, 3/6 antigen matched cord blood transplants.

We hope that our experience is helpful to the FDA as it develops regulatory requirements for cord blood banking and transplantation. Should there be any questions about the data or should further data be required, please contact us.

Respectfully submitted

Donna Wall

Donna Wall, MD
Director, St. Louis Cord Blood Bank

Attachments:
Appendix 1: Summary of Clinical Transplant Results with Cord Blood Units from the St. Louis Cord Blood Bank
Appendix 2: Summary of Cord Blood Transplant Results for Transplants Performed at Cardinal Glennon Children's Hospital.
Appendix 3: Correlation between measures of hematopoiesis

Appendix 1: Summary of Clinical Transplant Results with Cord Blood Units from the St. Louis Cord Blood Bank

Cord blood units from the SLCBB have been exported to 59 transplant programs in 23 states and 12 countries.

Table 1. Characteristics of patients for whom cord blood units have been exported from the St. Louis Cord Blood Bank from 2/97 through 7/00 (n=161).

	Frequency	%
CBU recipient status		
Alive	82	
Expired	42	
CBU infused- post thaw report received only	7	
CBU exported- no indication of infusion	13	
CBU exported-not infused	9	
UCB infused within 2 months-pending follow-up	8	
Recipient gender		
Female	78	49
Male	81	50
Unknown	2	1
Recipient ethnicity		
Caucasian	109	68
African American	8	5
Mediterranean	3	2
Hispanic	16	10
American Indian	2	1
Indian	1	<1
Pacific Islander	1	<1
Unknown	21	13
Diagnosis		
ALL	44	27
AML/MDS	38	23.6
Lymphoma	7	5
CML	8	6
JMML	3	1.7
Multiple myeloma	1	0.5
Other leukemias	3	1.7
Neuroblastoma	1	0.5
Breast cancer	1	0.5
Aplastic Anemia	14	8.6
Hemoglobinopathy	2	1
Storage/metabolic disorders	18	11
Severe combined immunodeficiency	13	8
Other Immunodeficiencies	8	6

Table 2 . Weight and age of patients (n=~~112~~ 111 DW)

	Weight (kg)	Age (yrs)
Mean	31	11
Std. Dev.	26	14
Median	22	7
Min.	4	0.1
Max.	114	55
Quartiles		
25	11	1.5
50	22	7
75	45	13

Table 3. Total Nucleated Cell (TNC) dose and CD34+ cell dose transplanted

	TNC (10^7/kg)	CD34 (10^5/kg)
Mean	8.0	4.5
Std. Dev.	7.0	2.7
Median	6.0	5.4
Min.	1.2	0.2
Max.	40.0	30.4
Quartiles		
25	3.0	1.3
50	6.0	2.7
75	11.0	5.3
N	111	110

Table 4: HLA matching and GVHD post transplant

	FREQUENCY	%
HLA match		
6/6	17	11
5/6	76	47
4/6	63	39
3/6	5	3
N	161	
Grade of Acute GVHD		
0	27	31
1	14	16
2	17	19.5
3	11	12.6
4	6	6.8
Not evaluable – early death	12	13.7
Not evaluable – no data submitted/less than 3 months post transplant	80	49.6
Evidence of Chronic GVHD		
None	34	28
Yes-Limited	5	4.1
Yes-Extensive	4	3.3
Yes-not graded	1	0.8
Not documented	1	0.8
Not evaluable – early death	6	4.9
Not evaluable – no data submitted/< 1 year post transplant	110	51.6

Figure 1: Overall survival of cord blood transplants performed using units from the St. Louis Cord Blood Bank

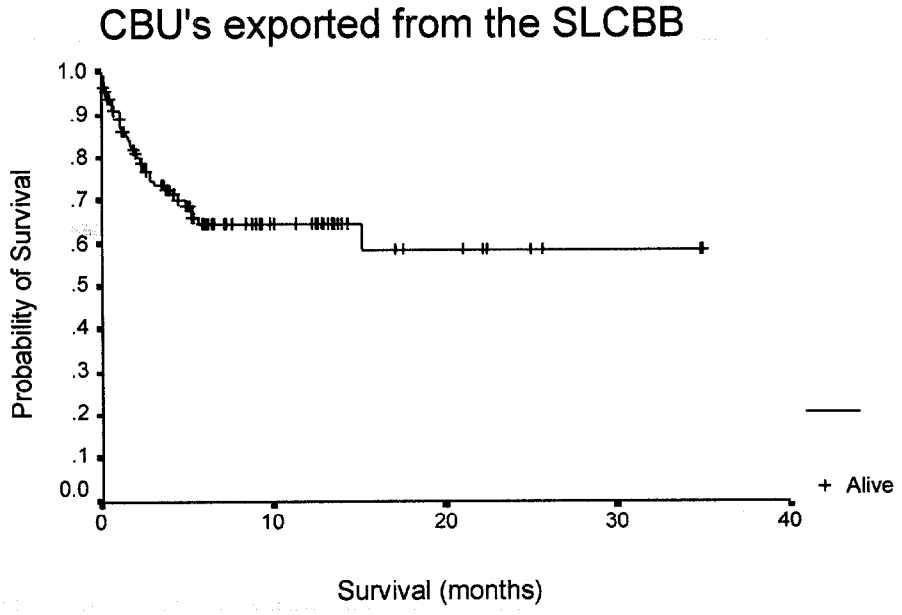


Figure 1. Includes 111 CBU transplants. Age of cryopreserved cord blood used ranges from 4 mos to 3.7 years. (7/5/00)

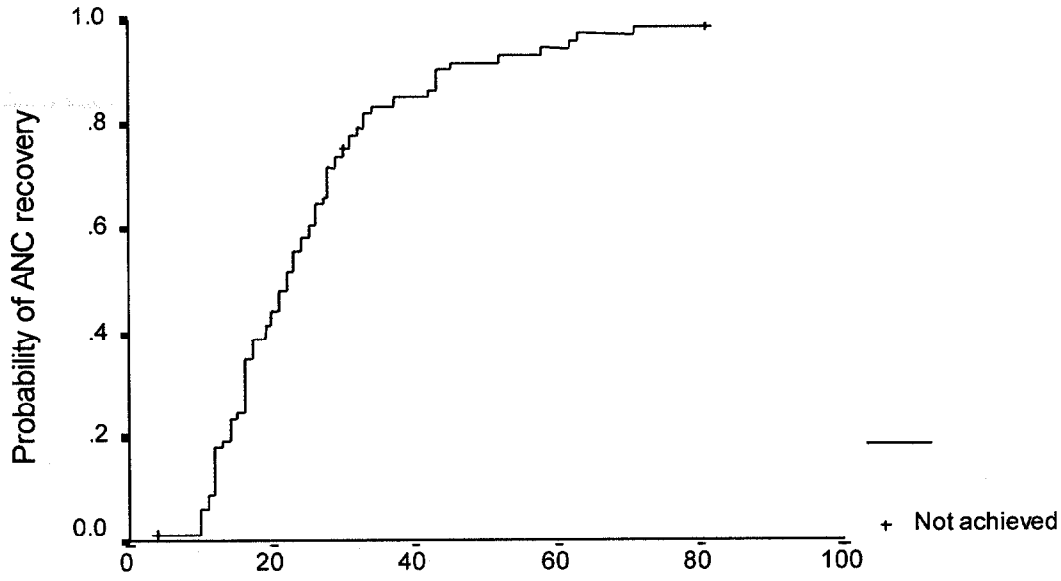
For the analysis of survival and engraftment only units minimally manipulated were evaluated. There have been 8 units released for expansion protocols. Six have been used in transplantation at this point (2 patients are alive at this time). Additionally units used emergently for treatment of primary graft failure are not included in this analysis. Transplants were evaluable for neutrophil recovery if the patient survived greater than 60 days and for platelet recovery if they survived over 100 days.

Descriptive statistics and Kaplan-Meier survival analyses were assessed using the SPSS software package (version 9.0). Censorship of survival data is defined as the date of last follow-up report received from the transplant center.

Table 5. Recovery of neutrophil and platelet count post cord blood transplant

	ANC >500 (days)	**Platelet>20** (days)	**Platelet>50** (days)
Mean	25	61	70
Std. dev.	15	32	30
Median	22	53	62
Min.	2	4	25
Max.	81	154	136
Percentiles			
25	14	42	48
50	22	53	62
75	30	81	92
N	79	59	37

Figure 2: Overall neutrophil recovery

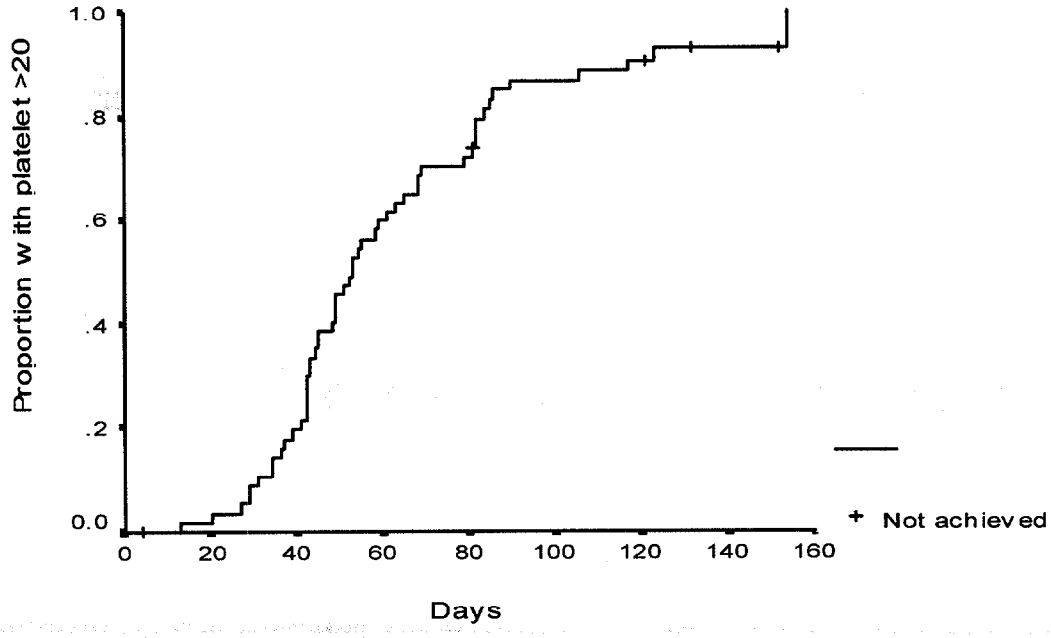


Days to ANC>500

N = 78 transplants.

7/5/00

Figure 3: Overall platelet recovery



We analyzed the impact of cell dose on neutrophil and platelet recovery as well as survival. What follows is analysis based on total nucleated cell (TNC) per kg body weight of transplant recipient. The cut points of 2 x 10^7/kg, 3 x 10^7/kg, 5 x 10^7/kg and 1 x 10^8/kg were analyzed. It is appreciated that we have few transplants performed with fewer than 2 x10^7/kg (only 5 transplants), but present the data that we have.

Figure 4a: Neutrophil recovery for transplants with <2 x10^7 TNC/kg compared to ≥2 x 10^7/kg

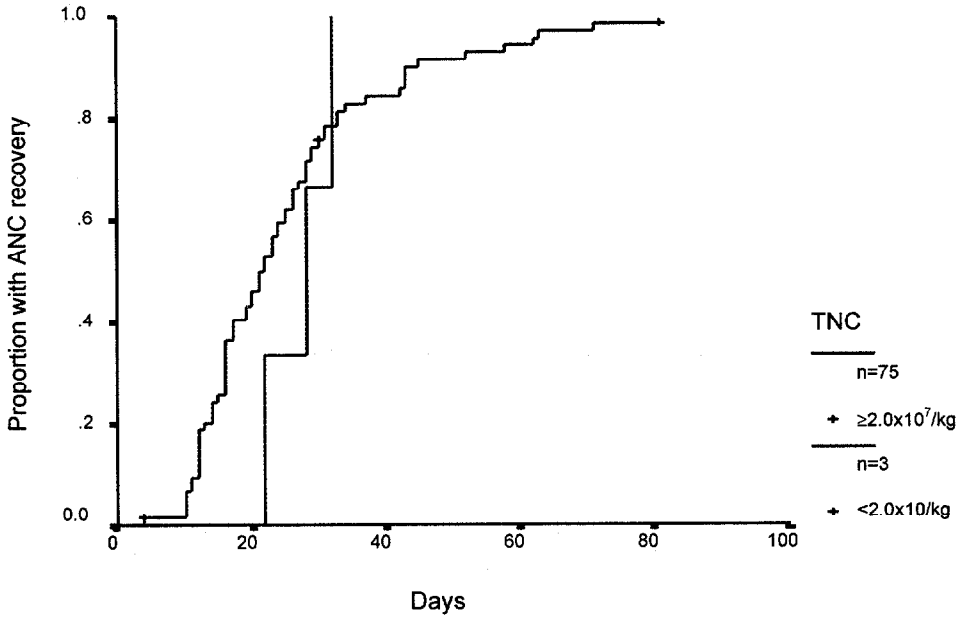
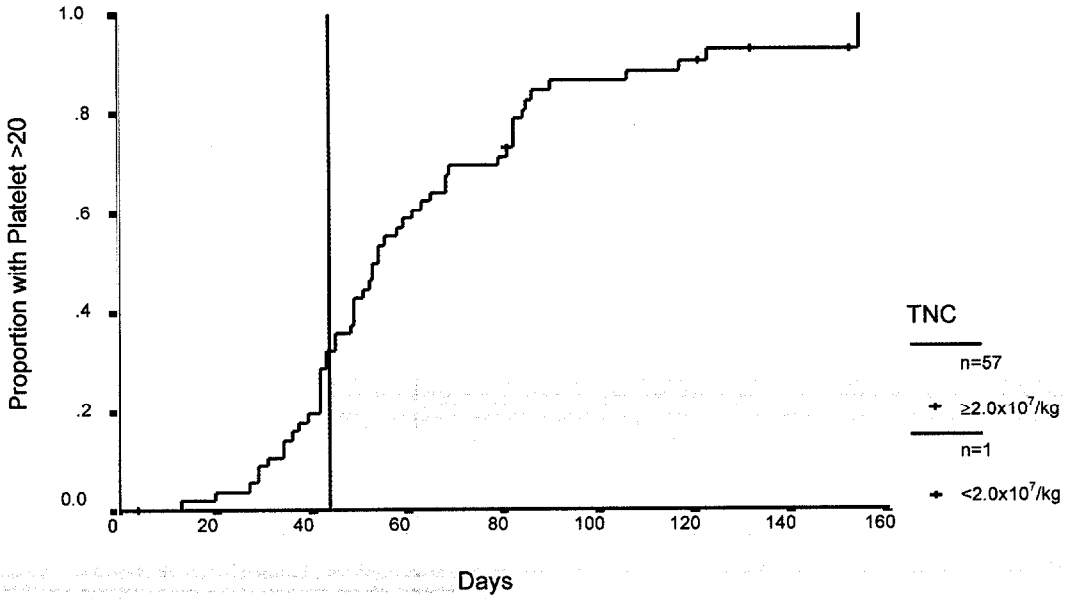


Figure 4b: Recovery of platelets to >20,000 for transplants with <2 x10^7 TNC/kg compared to ≥2 x 10^7/kg



4c: Survival based on transplants with <2 x10^7 TNC/kg compared to ≥2 x 10^7/kg

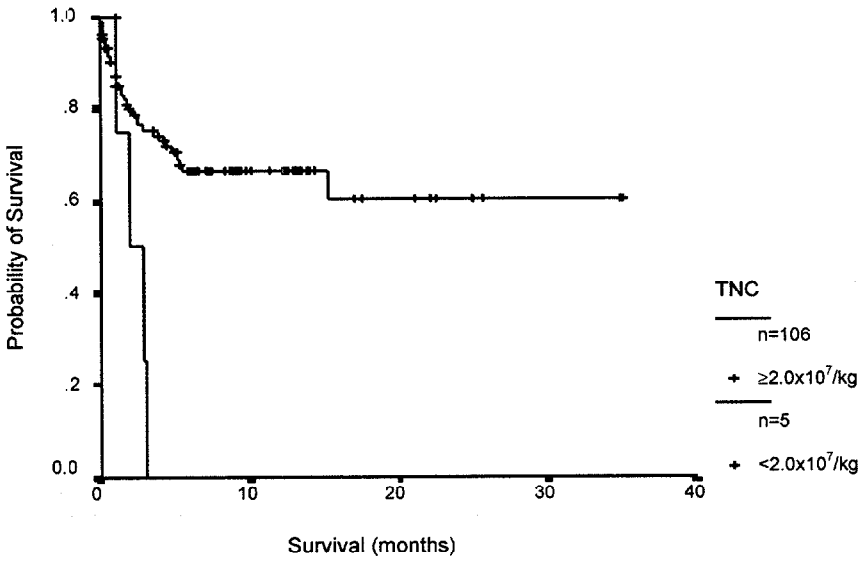


Figure 5a: Neutrophil recovery for transplants with <3 x10^7 TNC/kg compared to ≥3 x 10^7/kg

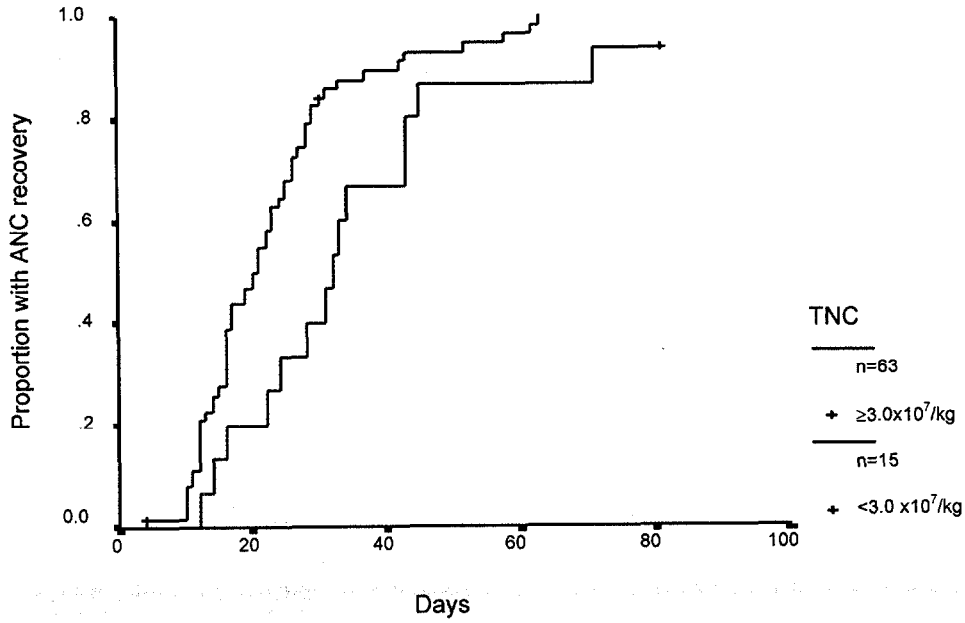


Figure 5b: Platelet recovery for transplants with <3 x10^7 TNC/kg compared to ≥3 x 10^7/kg

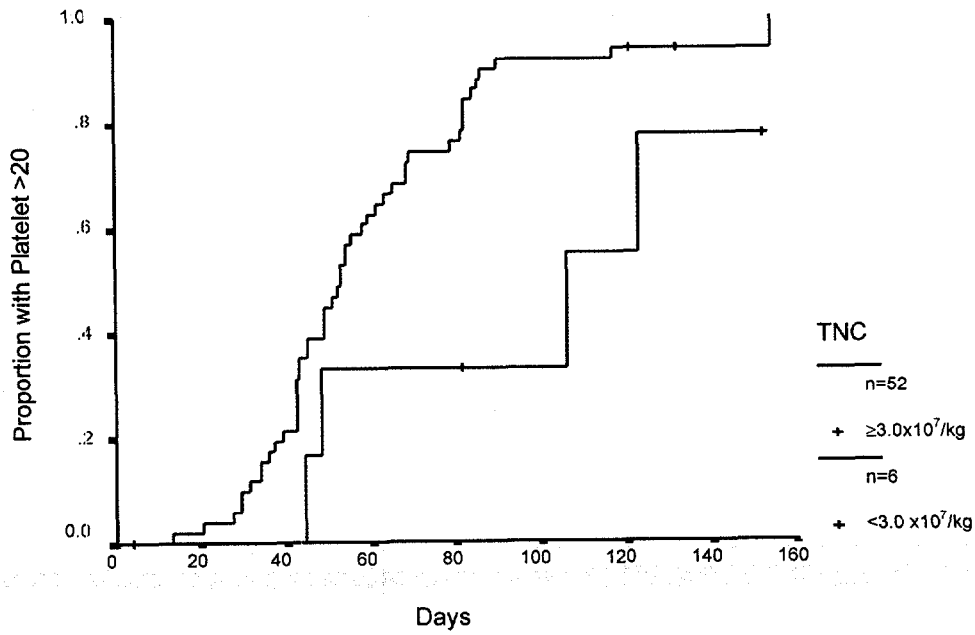


Figure 5c: Survival for transplants with <3 x10^7 TNC/kg compared to ≥3 x 10^7/kg

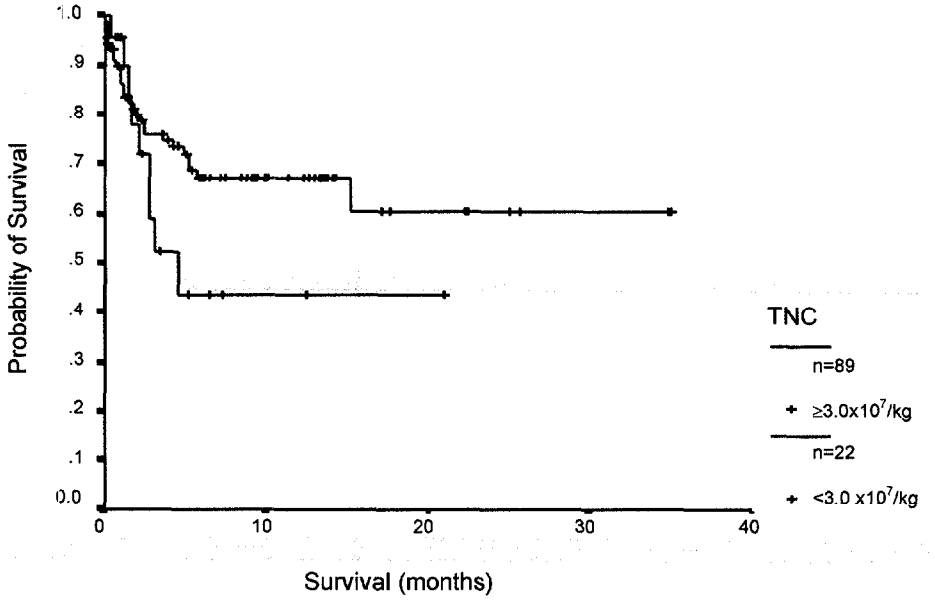


Figure 6a: Neutrophil recovery for transplants with <5 x10^7 TNC/kg compared to ≥5 x 10^7/kg

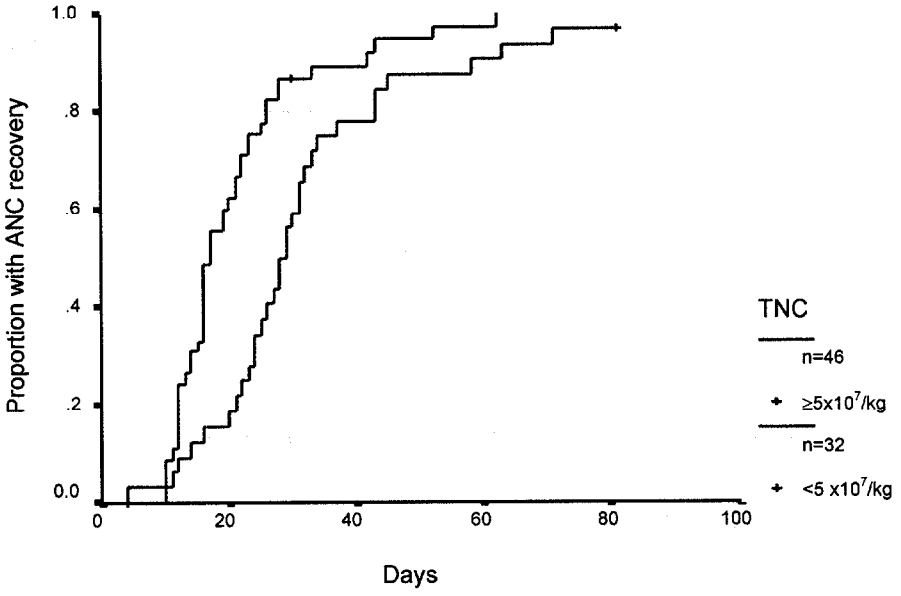


Figure 6b: Platelet recovery for transplants with <5 x10^7 TNC/kg compared to ≥5 x 10^7/kg

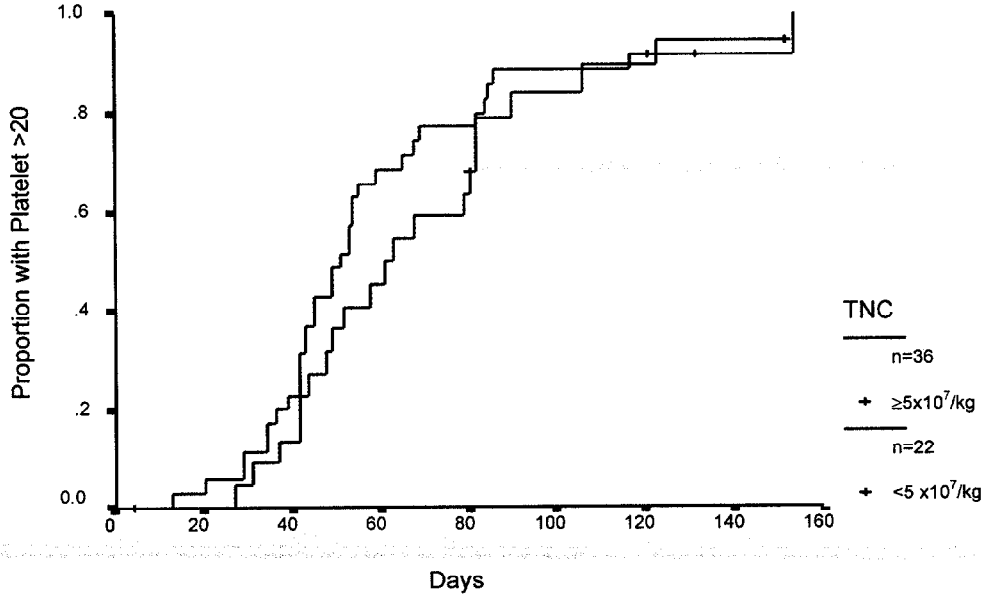


Figure 6c: Survival for transplants with <5 x107 TNC/kg compared to $\geq 5 \times 10^7$/kg

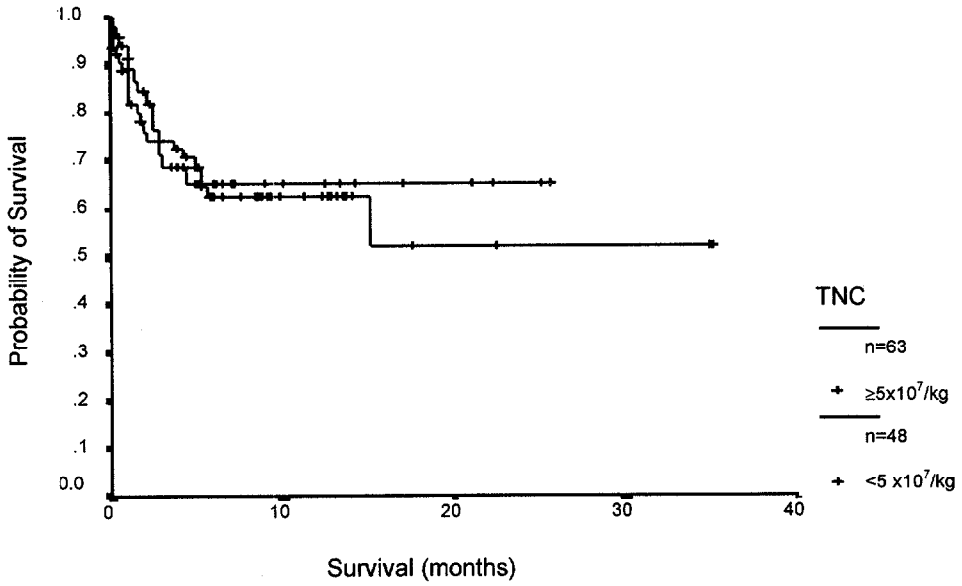


Figure 7a: Neutrophil recovery for transplants with <1 x10^8 TNC/kg compared to ≥1 x 10^8/kg

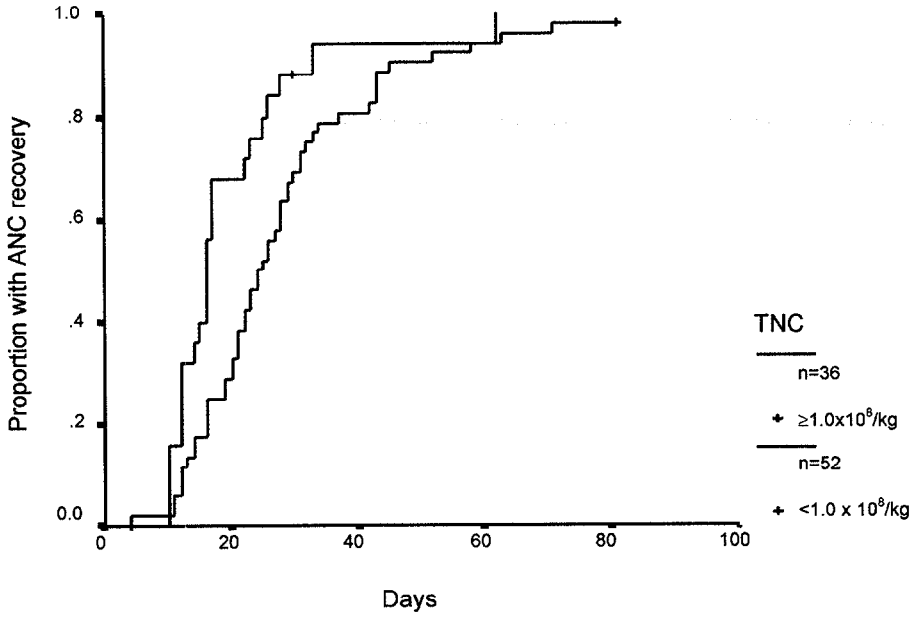


Figure 7b: Platelet recovery for transplants with <1 x10^8 TNC/kg compared to ≥1 x 10^8/kg

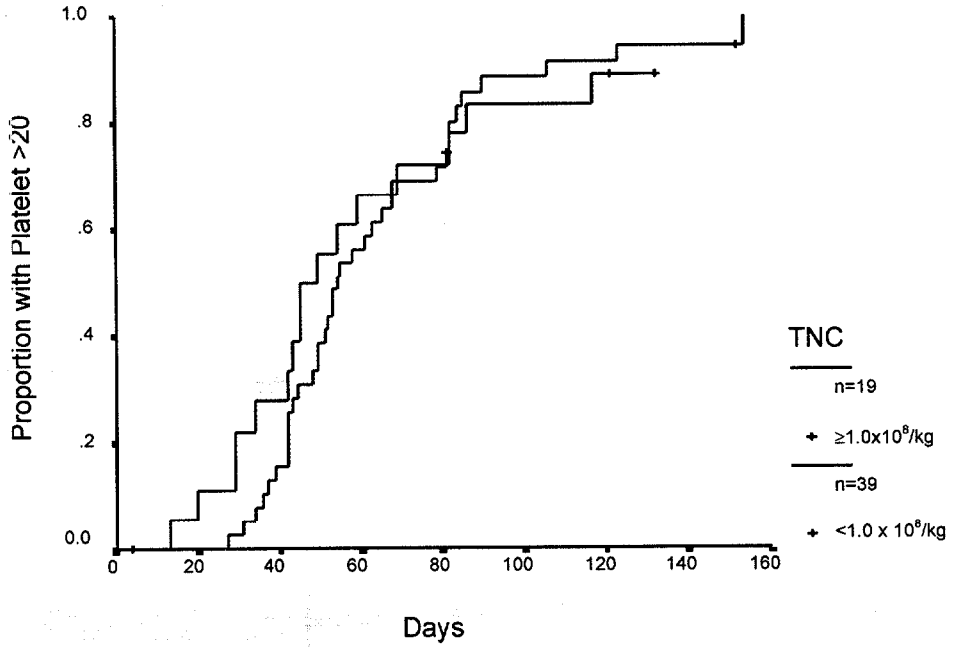


Figure 7c: Survival for transplants with <1 x10^8 TNC/kg compared to ≥1 x 10^8/kg

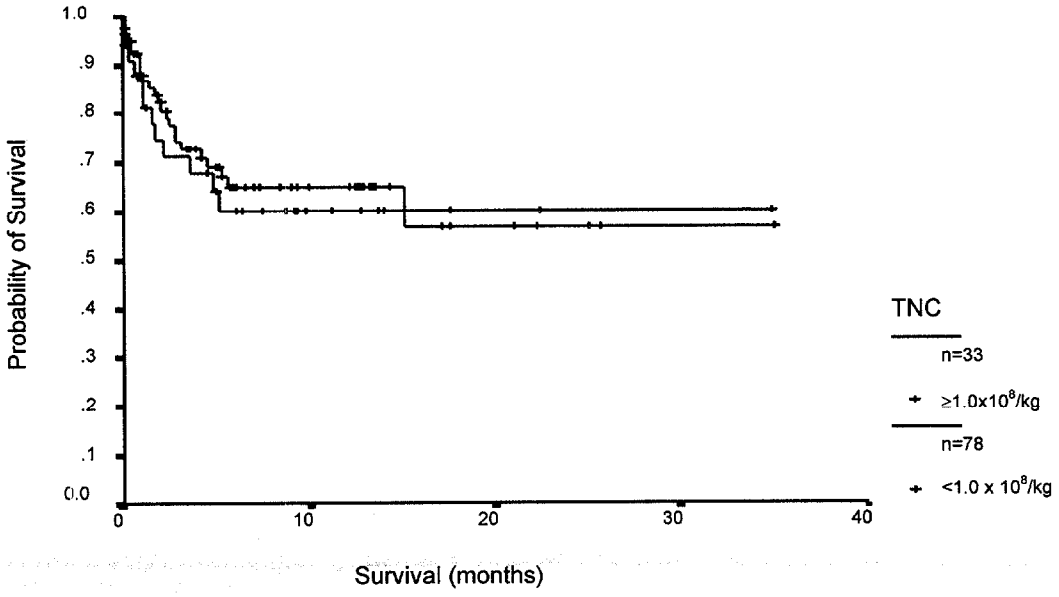
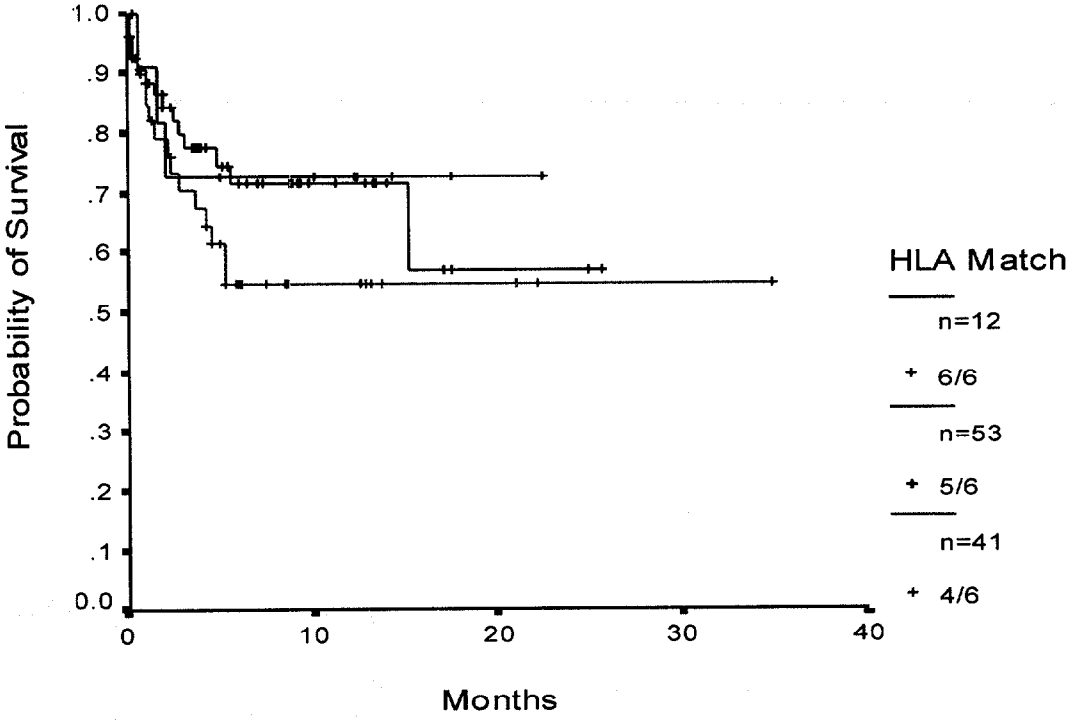


Figure 8: Lack of impact of HLA matching on survival



Appendix 2: Summary of Cord Blood Transplant Results for Transplants Performed at Cardinal Glennon Children's Hospital.

Table 1. Patient demographics of cord blood transplant recipients at CGCH (n=39)

	Frequency	%
Recipient status		
Alive	26	67
Expired	13	33
Recipient gender		
Male	21	54
Female	18	46
Recipient ethnicity		
Caucasian	33	85
African American	5	13
East Indian	1	2
Diagnosis		
ALL	9	23
AML	6	15
Neuroblastoma	1	2
Aplastic anemia	5	13
Hemoglobinopathy	1	2
Storage metabolic disorder	5	13
SCIDS	10	25
Other immune deficiencies	3	7

Table 2: Weight and age of transplant recipients

	Weight (kg)	Age (yrs)
Mean	19	5.0
Std. dev.	17	4.7
Median	14	3.4
Min.	3	0.1
Max.	69	15.6
Percentiles		
25	8	0.7
50	14	3.4
75	22	8.1

Table 3: Cell dose and CD34+ cell dose of infused cords

	TNC (10^7/kg)	CD34 (10^5/kg)
Mean	13.4	7.6
Std. Dev.	12.7	8.9
Median	9.1	4.2
Min.	2.0	0.9
Max.	6.5	30.4
Percentiles		
25	4.7	1.2
50	9.1	4.2
75	19.3	10.2

Table 4: HLA typing and GVHD - CGCH

	Frequency	%
HLA match		
3/6	3	8
4/6	18	45
5/6	14	35
6/6	5	12
Acute GVHD		
None	10	27
Grade I	12	29
Grade II	5	13
Grade III	10	26
Grade IV	1	2
Not evaluable	1	2
Chronic GVHD		
No	17	45
Yes-limited	6	16
Yes-extensive	1	3
Not evaluable	15	36

Figure 1 : Overall survival for cord blood transplants performed at CGCH

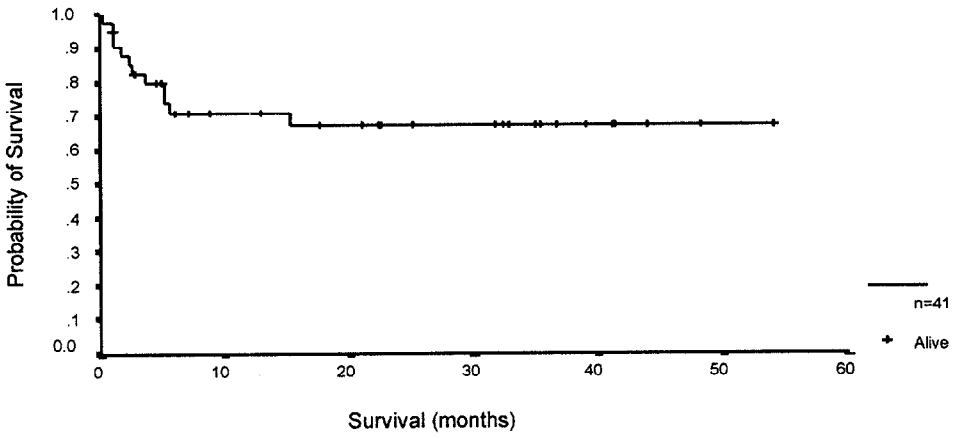


Figure 2 : Time to neutrophil recovery - CGCH

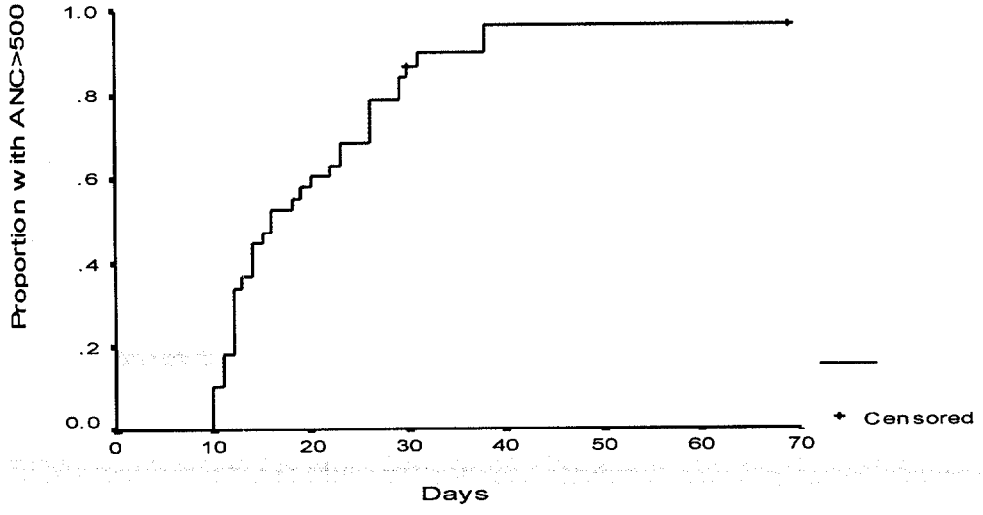


Figure 3 : Time to platelet recovery post cord blood transplant - CGCH

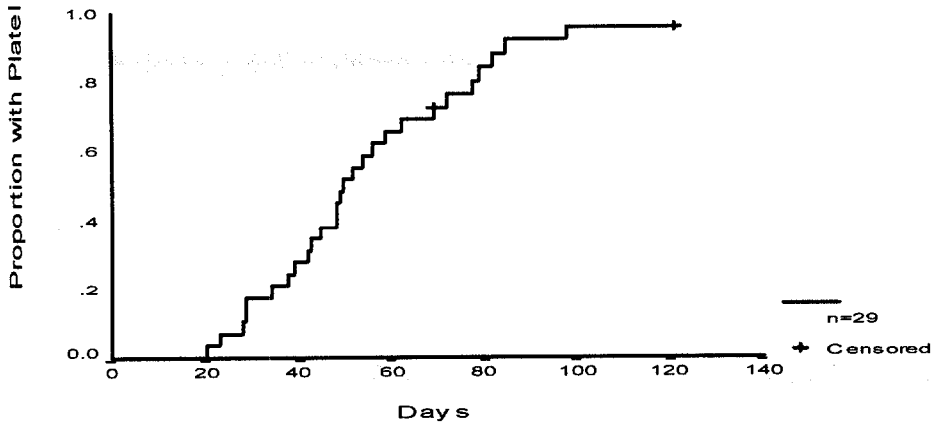
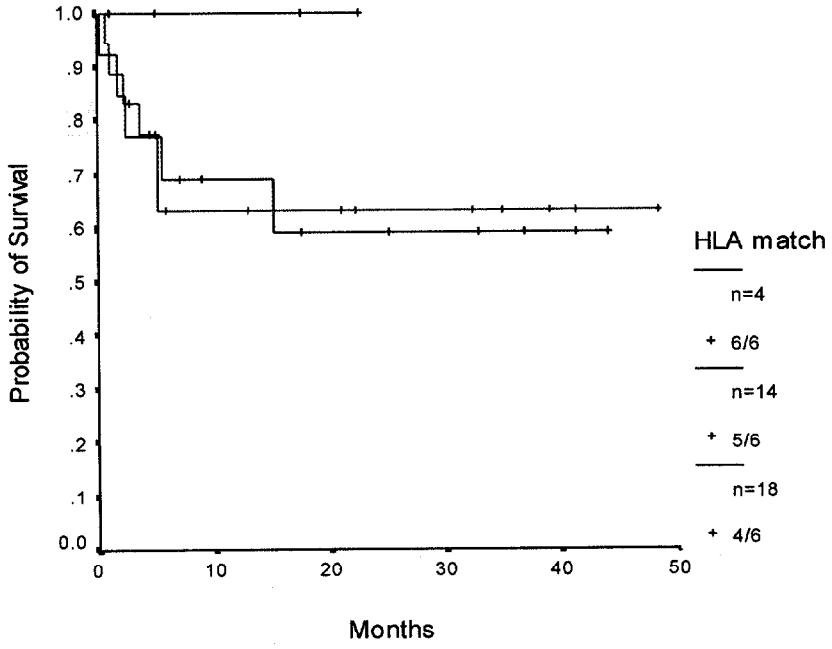


Figure 4 : Lack of impact of HLA matching on transplant outcome - CGCH



Appendix 3. Correlation between measures of hematopoiesis

Background: Unrelated donor cord blood (UCB) is rapidly becoming accepted as an alternative source of hematopoietic stem cells, but is limited by the number of stem cells available to reconstitute a given donor. Surrogate measures of hematopoietic stem cells such as total nucleated cell (TNC), total CD34+ cells (CD34+), or total colony forming units (CFU)/kg of recipient are utilized when selecting a unit. There is, in general, a good correlation between these measures of hematopoiesis (TNC vs. CD34, r= 0.58; TNC vs. CFU, r= 0.78; CD34 vs. CFU, r= 0.60). However there are CBU's where the CD34 or CFU enumeration is disproportionately high or low for a given TNC(see figure 1a and 1b.). We examined such units in an attempt to assign hematopoietic potential, both for the unit selection process and for the development of banking criteria for exclusion of cord blood units with poor hematopoietic potential.

Of 2,309 UCBs studied with TNC, CFU and CD34 analysis, two groups were identified (see figures 2a and 2b.): A – units with CD34 counts >2SD above the expected for a given TNC (n=15); B – units with CD34 counts >2SD below expected (n=81). When groups A and B were examined for CFU vs TNC, 80% of group A and 100% of group B CFU counts were within the 95% CI of the predicted range – thus the CD34 count failed to identify units with superior or inferior hematopoiesis. These results highlight the difficulty in assessing hematopoietic potential based on CD34 count.

Figure 1a. Correlation of TNC with CD34 in cord bloods

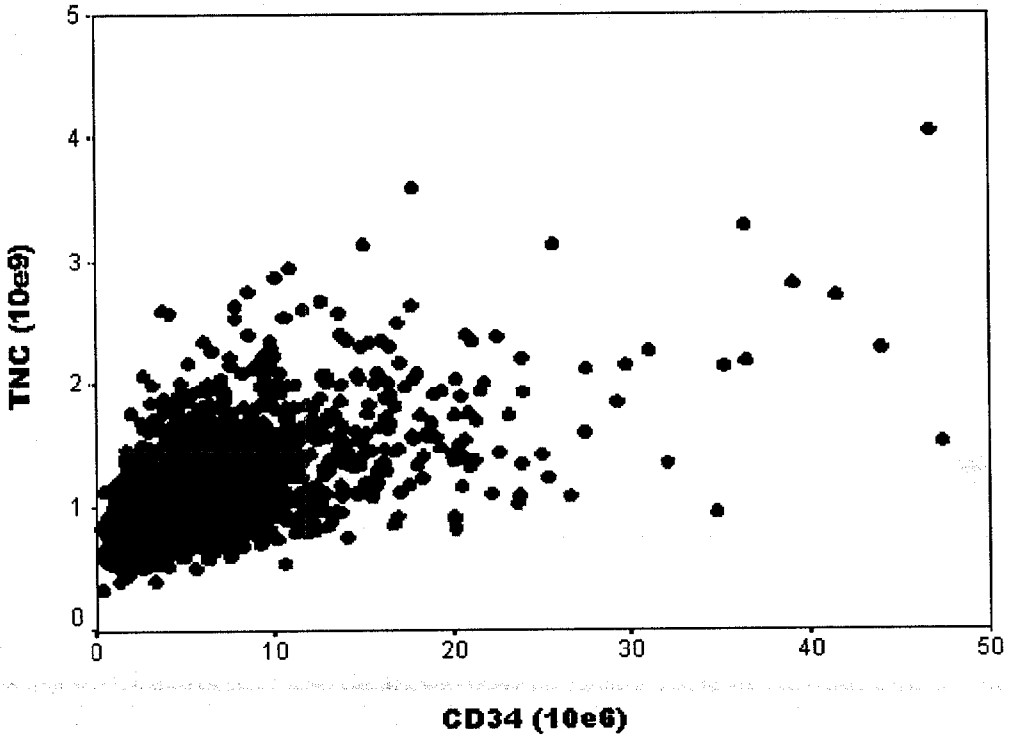


Figure 1b. Correlation of TNC with CFU in cord bloods

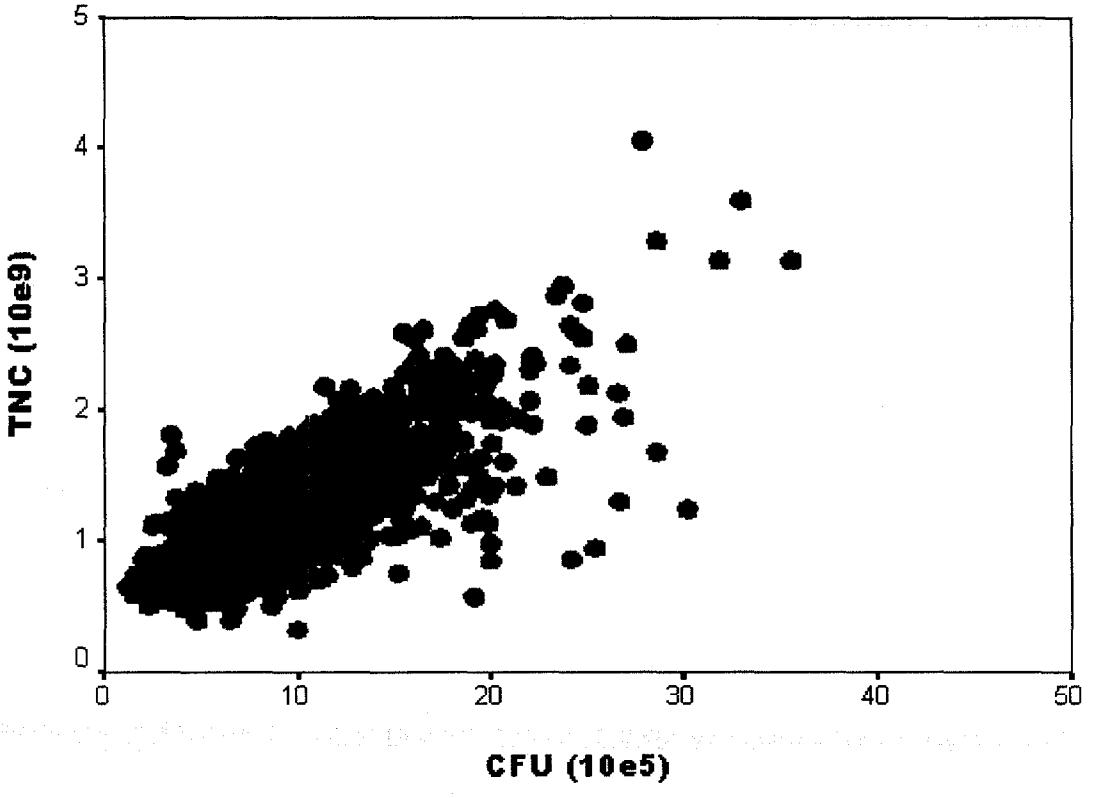


Figure 2a. Comparison of the absolute CFU counts between 3 categories of CD34 counts in banked cord bloods

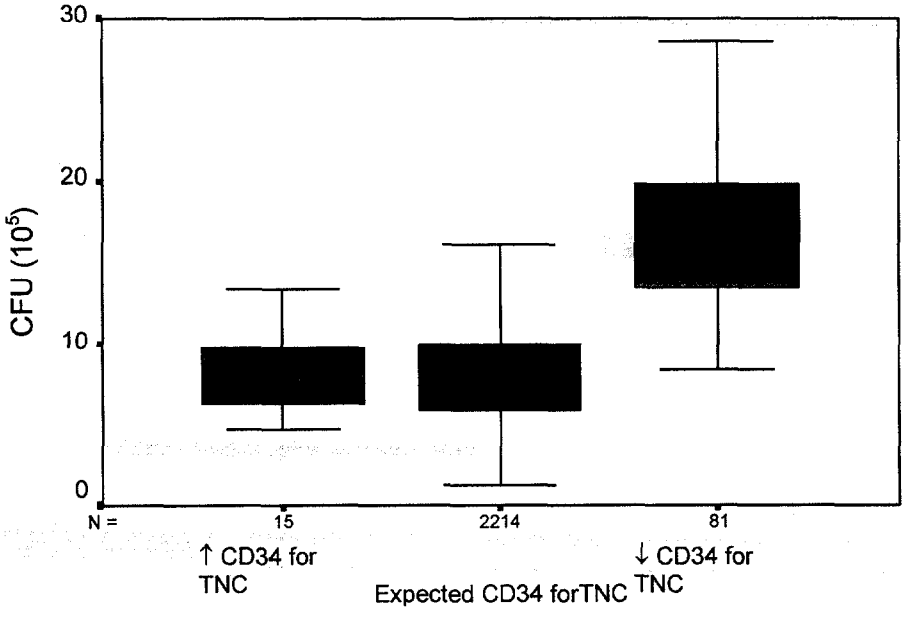
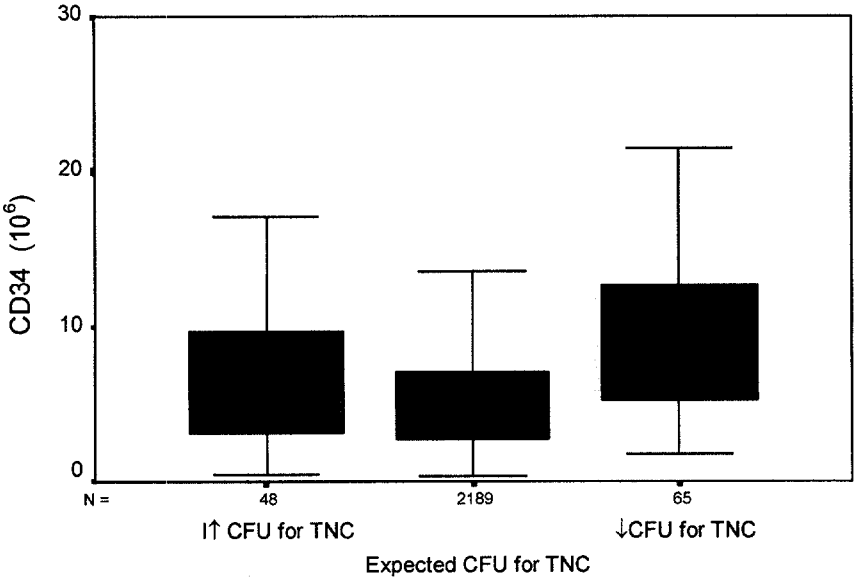


Figure 2b. Comparison of the absolute CD34 counts between 3 categories CFU counts in banked cord bloods.



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